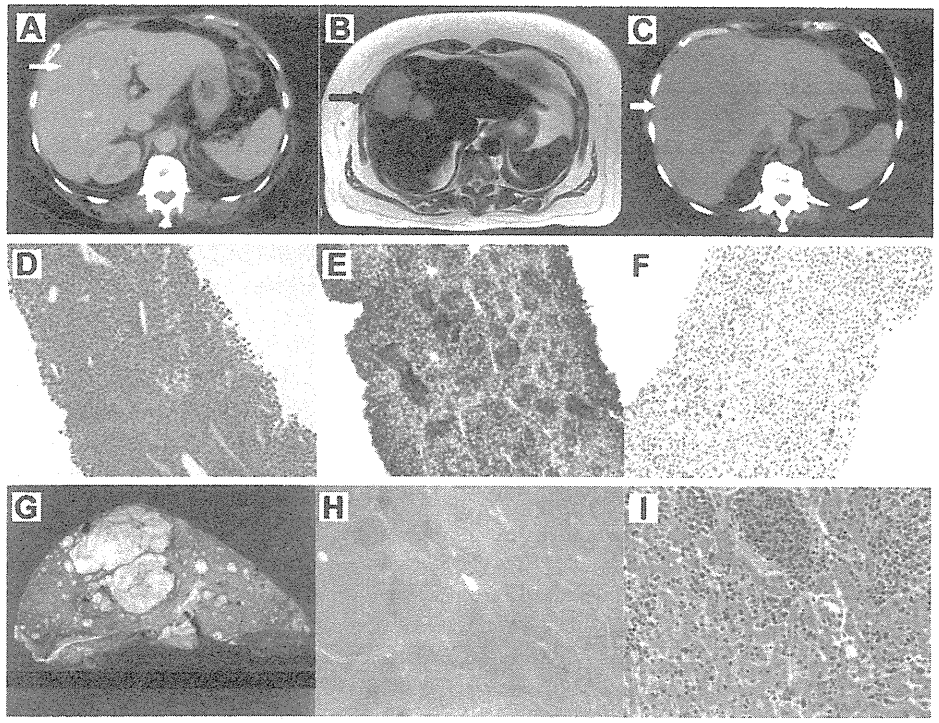
Figure 1 Hepatic Extramedullary Disease (Arrows). (A) CT Scan in April 2011 Showing a Small Solid Lesion Measuring 9 mm in the Liver S8 (Right Anterior Superior Segment). (B) Abdominal MRI in July 2011 Showing Multiple Lesions in The Liver Without Hepatomegaly, Which Were Hyperintense on T2-Weighd Images. (C) CT Scan in October 2011 Showing That the Hepatic Lesion Had Increased In Size to 117 mm. (D-F) Histological and Immunohistochemical Studies of a Hepatic Nodular Lesion Showing Sheets of Plasma Cells (D; H&E Stain) That Were Positive for CD138 (E). Myeloma Cells Were Also Positive for p53 (DO-7, A Mouse Monoclonal Antibody Which Recognized the Wild-Type and Mutant-Type of the p53 Protein; F). (G-I) Autopsy Specimen of the Enlarged Liver in October 2011 Showing Numerous Nodular Lesions (G and H). Myeloma Cells Also Proliferated in the Sinusoids (I)



Abbreviations: CT = Computed Tomography; H & E = Hematoxylin and Eosin; MRI = Magnetic Resonance Imaging.

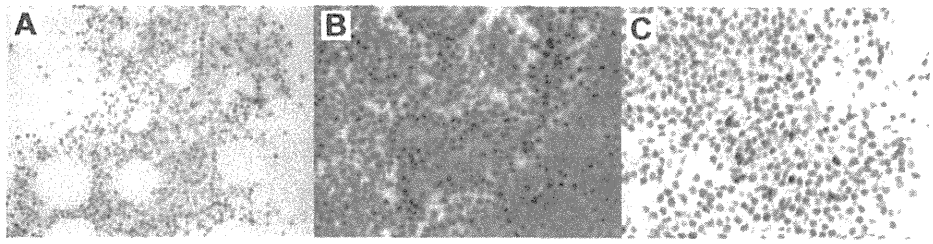
November 2010 revealed 89.4% plasma cells with anaplastic features. Metaphase cytogenetics showed a complex karyotype: 79, XXX, +2, +3, +5, add(6)(q13), -8, +9, add(12)(q24.1)x2, -13, -14, -16, -16, -17, -17, -18, -20, -20, +21, +22, +14mar (mar: Marker Chromosome). Fluorescence in situ hybridization analysis revealed hemizygous 17p13.1 (p53) deletion in 52.0% of the analyzed cells. Although lenalidomide and dexamethasone halved serum LDH and urine M protein, bone marrow aspiration became a dry tap.

Table 1 Summary of Diagnostic Findings and Treatments Over Time

Date, Month/Year	LDH, IU/L[a]	β_2MG, mg/L[b]	Urine M-Protein, g/24 Hours	BM Plasma Cells, %	BM Cytogenetics, G-Banding	BM 17p Deletion in FISH Analysis, %	Hepatic EMD, mm	Treat-ment Regimen
2/2008	398	—	—	9.2	—	—	—	—
6/2008	327	5.3	15.3	—	—	—	—	BD
5/2009	213	2.1	<0.1	1.4	46,XX	—	—	BD
6/2010	353	5.8	5.0	—	—	—	—	TD
11/2010	479	10.8	7.8	89.4	Complex	52.0	—	Rd
4/2011	263	5.8	5.2	Dry tap	—	—	9	Rd with Mel
7/2011	365	8.6	9.6	—	—	—	57	REP
10/2011	850	20.8	40.5	Dry tap	—	—	117	BD

Abbreviations: β_2MG = β_2 microglobulin; BD = bortezomib/dexamethasone; BM = bone marrow; EMD = extramedullary disease; FISH = fluorescence in situ hybridization; G-banding = Giemsa banding; LDH = lactate dehydrogenase; Mel = melphalan; Rd = lenalidomide/low-dose dexamethasone; REP = lenalidomide/cyclophosphamide/prednisolone; TD = thalidomide/dexamethasone.
[a]Lactate dehydrogenase normal range, 80 to 200 IU/mL.
[b]β_2 microglobulin normal range, 1.0 to 1.9 mg/L.

Figure 2 Bone Marrow Clot Sections. (A) Immunohistochemistry in February 2008 Showing That Bone Marrow Myeloma Cells Were Negative for P53. (B and C) Bone Marrow Myeloma Cells in November 2010 Showing an Anaplastic Morphology (B) That Converted to Positive for p53 (C)



Computed tomography (CT) scans taken during the post-operative follow-up for uterine cancer in April 2011 showed 2 nodular lesions measuring 9 mm in the liver, which were suspected to be metastatic carcinoma or fungal abscess (Figure 1A). Abdominal magnetic resonance imaging (MRI) 3 months later revealed multiple new lesions that had increased in size to 57 mm and appeared hypointense on T1- and hyperintense on T2-weighed images (Figure 1B). Ultrasound-guided biopsy of the lesion revealed the massive infiltration of monoclonal plasma cells (Figure 1D and E). These cells were positive for the expression of p53 using immunohistochemistry (Figure 1F). Neither melphalan nor cyclophosphamide combined with lenalidomide was effective (Figure 1C). Transfusion-resistant severe pancytopenia deteriorated. The patient died in October 2011, when her serum LDH was 850 IU/L, β2 microglobulin was 20.8 mg/L, and urine M protein was 40.5 g per 24 hours (Table 1). Liver function remained almost normal until her death. At autopsy numerous yellowish nodular lesions composed of myeloma cells in the liver were observed (Figure 1G and H), which corresponded with the findings observed on CT and MRI images. In addition, myeloma cells proliferated in the sinusoids (Figure 1I). The extensive infiltration of myeloma cells into the bone marrow and spleen were also observed.

Discussion

Marked improvements have been reported in the prognosis for patients with MM in the past decade, that have been attributed to the introduction of novel agents such as bortezomib, thalidomide, and lenalidomide. An increase in the incidence of second primary malignancy has also emerged with the prolongation of survival.[8] Munker et al reported that the incidence of malignancies before the diagnosis of MM occurred and that of second malignancies were elevated in MM patients.[9] Our patient was diagnosed with uterine cancer and MM simultaneously. However, the factors that induce or favor the occurrence of other malignancies in MM patients remain unknown.[8]

Although the incidence of hepatic EMD in MM is relatively high on autopsy case series,[10] it is rarely clinically evident pre-mortem.[11] Our patient initially presented with small nodular lesions in the liver that mimicked metastatic cancer or fungal abscess. Hepatic EMD commonly presents as a diffuse infiltration with hepatomegaly on imaging and rarely as unifocal or multifocal nodules.[12] Two histological patterns of hepatic infiltration by plasma cells have been described: diffuse (sinusoidal or portal) and nodular, with the diffuse pattern being more frequently observed than the nodular pattern.[13,14] Several case reports described that nodular hepatic EMD was associated with end-stage disease and a very poor prognosis.[12,15,16] In contrast, hepatic EMD in our patient appeared to have changed from a nodular to a nodular and diffuse sinusoidal pattern at the end-stage. Corresponding findings of pre-mortem images and autopsy of hepatic EMD such as those in our case have not been reported.

The deletion of 17p13.1, the tumor suppressor gene p53 locus, has been detected in 10% of MM patients at diagnosis and increases in prevalence with disease progression. Patients with this deletion have aggressive features such as EMD, the lack of a treatment response, and shorter survival even in this novel agent era.[17,18] Chang et al demonstrated that the aberrant nuclear expression of the p53 protein detected using immunohistochemistry was strongly associated with a hemizygous p53 deletion and an adverse outcome of MM.[19] Sheth et al indicated that the nuclear expression of p53 was associated with disease progression from intramedullary to extramedullary sites in MM.[20] Immunohistochemistry revealed that bone marrow myeloma cells in our patient were negative for the expression of p53 at diagnosis, but were positive at disease relapse (Figure 2). Therefore, the development of hepatic EMD in our case appears to have been related to p53 deletion, which originated through clonal evolution.

Conclusion

We here reported a case with MM that exhibited the rare and interesting presentation of nodular hepatic EMD. Nodular hepatic lesions enlarged rapidly despite novel agent-based therapy, resulting in nodular and diffuse infiltration. The results obtained in cytogenetic and immunohistochemical examination of myeloma cells suggested that the aggressive behavior of this case appears to have been related to the development of 17p deletion. Improved therapeutic strategies are required for this subgroup of patients with EMD. Although some reports demonstrated successful management of soft tissue EMD with novel agents,[21,22,23] it was not the case in our patient. The administration of multiagent chemotherapy, such as a CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)-like regimen which is used to treat aggressive B-cell

lymphoma, might be an option because of the high proliferation of cells that is associated with EMD.[4] Short et al showed that EMD responded to the new immunomodulatory drug pomalidomide with a response rate of approximately 30%.[24]

Disclosure

The authors have stated that they have no conflicts of interest.

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